# Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy

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**Supplementary materials:**

# The association between obstructive sleep apnea on diabetic kidney disease: a systematic review and meta-analysis

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**Table 1:** Eligibility criteria for systematic review

| Inclusion criteria | Exclusion criteria |
|---|---|
| *Participants:*<br>All adults with type 1 or type 2 diabetes mellitus (DM) | Children and adolescents (age below 18 years)<br>Pregnant females<br>Gestational diabetes mellitus<br>Maturity onset diabetes of the young<br>Latent autoimmune diabetes of adulthood<br>No type 1 or type 2 DM |
| *Exposure:*<br>Those with obstructive sleep apnea (OSA) or chronic intermittent hypoxemia (CIH) | Hypoxemia secondary to other respiratory disorders<br>Chronic obstructive pulmonary disease<br>Central sleep apnea<br>Heart failure<br>Asthma |
| *Comparator:*<br>Adults without OSA or CIH | |
| *Outcomes:*<br>Diabetic kidney disease (micro- and macro-albuminuria and chronic kidney disease assessed using glomerular filtration rate) | Renal impairment secondary to non-DM causes |
| *Study designs:*<br>Cross sectional study<br>Cohort study<br>Case series | Non-human studies<br>Single case reports<br>Sample size < 10 participants<br>Randomised controlled trials<br>Intervention studies<br>Experimental studies<br>Systematic reviews/reviews<br>Editorials<br>Protocol papers<br>Letters<br>Guidelines/consensus statements |
| *Language:*<br>All languages | |

**Search strategy:**

**Table 2:** Search terms for MEDLINE, EMBASE and Cochrane Database

| Search terms for diabetic kidney disease |
|---|
| 1. Diabet$.mp. |
| 2. Respiratory system/ or breathing disorder/ or snoring/ or hypoventilation/ or sleep/ or polysomnography/ or sleep apnea syndrome/ or breathing/ or sleep disordered breathing/ or sleep disorder/ |
| 3. Hypoxemia/ or respiratory function disorder/ or anoxia/ or hypoxia/ |
| 4. Somnolence/ or apnea/ or apnea hypopnea index/ or hypopnea.mp. |
| 5. 2 or 3 or 4 |
| 6. 1 and 5 |
| 7. Nephropathy.mp. or kidney disease/ |
| 8. Albuminuria.mp. or proteinuria/ or albuminuria/ |
| 9. $albuminuria.mp. |
| 10. Renal failure.mp. |
| 11. Kidney function/ |
| 12. Diabetic nephropathy/ or nephropa$.mp. or chronic kidney failure/ |
| 13. 7 or 8 or 9 or 10 or 11 or 12 |
| 14. 6 and 13 |

The free text used for OpenGrey database were “obstructive sleep apnea” and “obstructive sleep apnoea”

The search terms for Zetoc database included “obstructive sleep apnea and diabetes”, “obstructive sleep apnoea and diabetes”, “apnea and diabetes” and “apnoea and diabetes”.

**Table 3:** Quality assessment form

**Author:** **Year:** **Study ID:**
**Reviewer initials:**

| | Yes/No/ Unclear | Supporting evidence |
|---|---|---|
| **Selection bias** | | |
| 1. Does the study address an appropriate and clearly focused question? | | |
| 2. Does the study recruit consecutive patients? | | |
| 3. Are the cases and controls taken from comparable populations? | | |
| 4. Are the exclusion criteria the same for both cases and controls? | | |
| 5. Are the participants representative of the patient population? | | |
| 6. If applicable, is the control group comparable to cases (consider suitability, recruitment and baseline characteristics)? | | |
| 7. Is it clear that controls are not cases (in case control study)? | | |
| **Overall Judgement (Weak / Moderate /Strong)** | | |
| **Respiratory measurement** | | |
| 1. Did the study use a suitable measurement for OSA? (PSG/oximetry measured in standard, valid and reliable way) | | |
| 2. Is the scoring of the respiratory measures based on guidelines/consensus guidelines eg. AASM guidelines? | | |
| 3. Is there a clear definition of OSA? | | |
| **Overall Judgement (Weak / Moderate / Strong)** | | |
| **Blinding** | | |
| 1. Did the study blind the assessor performing the sleep analysis? | | |
| **Overall Judgement (Weak / Moderate / Strong)** | | |
| **Study methods** | | |
| 1. Are the attrition rates or missing data clearly documented? | | |
| 2. Did the study document the reasons for drop outs or missing data? | | |
| 3. Is this a retrospective or prospective design? | | |
| **Overall Judgement (Weak / Moderate / Strong)** | | |
| **Analysis** | | |
| 1. Are all the outcomes reported? | | |
| 2. Did the study adjust for confounding variables? | | |
| **Overall Judgement (Weak / Moderate /Strong)** | | |
| **Overall judgement for the study (Weak, Moderate, Strong)** | | |

**Table 4:** Criteria used for the diagnosis of obstructive sleep apnea and diabetic kidney disease assessment as reported by the included studies

| Study | Definition of apnea/hypopnea or oxygen desaturation (OD) | OSA diagnosis | Min recording | DKD test | DKD diagnosis |
|---|---|---|---|---|---|
| Buyukaydin 2012[1] | AASM criteria* | AHI≥5 events/hr | NA | 24 hour urine albumin | Albuminuria ≥ 30mg/day |
| Furukawa 2013[2] | OD ≥3% | ODI≥5 events/hr | 4 hours | Early morning urine ACR | Micro-albuminuria ≥3.4mg/mmol<br>Macro-albuminuria ≥ 34.0 mg/mmol |
| Kosseifi 2010[3] | NA | NA | NA | NA | Micro-albuminuria |
| Laaban 2009[4] | Apnea = increased variation in suprasternal pressure with no airflow for ≥10 seconds; hypopnea = ≥50% reduction in airflow with ≥4% desaturation for ≥ 10 seconds | AHI≥5 events/hr | NA | 24 hour urine albumin | Micro-albuminuria ≥ 30mg/day |
| Langrand 2014[5] | NA | NA | NA | NA | NA |
| Leong 2014[6] | AASM criteria* | AHI≥5 events/hr | 4 hours | eGFR | eGFR <60min/ml/1.73m$^2$ based on MDRD and CKD-EPI equations |
| Schober 2011[7] | Apnea = 80% reduction in airflow ≥ 10 seconds; hypopnea = 50-80% reduction in airflow with ≥ 4% desaturations for ≥ 10 seconds | AHI≥15 events/hr | NA | NA | NA |
| Storgaard 2014[8] | Apnea = 80% reduction in airflow ≥ 10 seconds; hypopnea = 50-80% reduction in airflow with ≥ 4% desaturations for ≥ 10 seconds | AHI≥5 events/hr | 4 hours | 24 hour urine albumin | Micro-albuminuria 30-300 mg/day<br>Macro-albuminuria > 300mg/day<br>(2 out of 3 samples |
| Tahrani 2013[9] | AASM criteria* | AHI≥5 events/hr | 4 hours | eGFR & urine ACR | MDRD eGFR <60min/ml/1.73m$^2$<br>ACR >3.4 mg/mmol |
| Tanaka 2009[10] | OD ≥3% | ODI≥5 events/hr | NA | Creatinine (mg/dl) | NA |
| Zhang 2014[11] | NA | AHI≥5 events/hr | NA | NA | NA |
| Zhang 2015[12] | Apnea = 80% reduction in airflow ≥ | AHI≥5 events/hr | NA | Urine ACR or medical | ACR >300mg |

| | | | |
|---|---|---|---|
| | 10 seconds; hypopnea = 50-80% reduction in airflow with ≥ 4% desaturations for ≥ 10 seconds | | history |

OD = oxygen desaturation, min = minimum, OSA = obstructive sleep apnea, hr = hour, NA = not available, DKD = diabetic kidney disease, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, ACR = albumin-creatinine ratio.*AASM = American Academy of Sleep Medicine criteria: apnea = complete cessation of airflow for ≥10 seconds; hypopnea = ≥30% reduction in airflow ≥4% drop in oxygen desaturation for ≥10 seconds.

**Table 5:** Summary of the results for diabetic kidney disease

| | **Diabetic kidney disease** |
|---|---|
| **OSA (based on AHI)** | 10 studies (n=2927)[1, 3-9, 11, 12]<br>Adjusted: (+) 3 studies[6, 9, 11]; (-) 0 studies<br><br>Unadjusted : (+) 1 studies[4]; (-) 6 studies[1, 3, 5, 7, 8, 12]<br>Pooled OR (7 studies[1, 4, 6-9, 12] – see Figure 1, supplementary materials)<br>1.59. 95% CI: 1.16 to 2.18 $I^2$= 26.8% |
| **OSA (based on ODI)** | 2 studies (n=1317)[2, 10]<br>Adjusted: (+) 2 study[2, 13]; (-) 0 studies<br>Pooled OR (2 studies[2, 10] – see Figure 3, supplementary materials)<br>2.00. 95% CI: 1.36 to 2.94 $I^2$= 0.0%<br><br>Pooled OR (4 studies[2, 9-11], combined AHI & ODI as OSA diagnosis – see Figure 2, main manuscript)<br>1.73, 95% CI: 1.13 to 2.64, $I^2$= 69.3%<br><br>Unadjusted: No data |
| **%TST<90** | 2 studies (n=158)[5, 6]<br>Adjusted: (+) 1 study[6]; (-) 0 study<br><br>Unadjusted: (+) 1 study[5]; (-) 0 study |
| **Mean $O_2$** | 2 studies (n=158)[5, 6]<br>Adjusted: (+) 0 study; (-) 1 study[6]<br><br>Unadjusted: (+) 1 study[5]; (-) 0 study |
| **Minimum $O_2$** | 3 studies (n=491)[3, 6, 9]<br>Adjusted: (+) 0 study; (-) 2 studies[6, 9]<br><br>Unadjusted: (+) 1 study[3]; (-) 0 study |

(+): reported significant association; (-): reported no significant associations; shaded cells indicate that no study reported data for the exposure-outcome combination. DR = diabetic retinopathy; OSA = obstructive sleep apnoea; AHI = apnoea-hypopnoea index; ODI = oxygen desaturation index; %TST<90 = percentage time spent under 90% oxygen saturation; $O_2$ = oxygen saturation, n = total number of participants

**Meta-analysis**

Three studies[3, 5, 11] did not report on their results therefore a meta-analysis was carried out for seven studies[1, 4, 6-9, 12] which reported unadjusted ORs on the association between OSA (defined using AHI) and DKD. The pooled estimates showed significant association (pooled OR 1.59, 95% CI: 1.16 to 2.18, $I^2$=26.8%, Figure 1) using random effects analysis. The funnel plot of these studies[1, 4, 6-9, 12] suggest an imbalance of small studies with positive results.

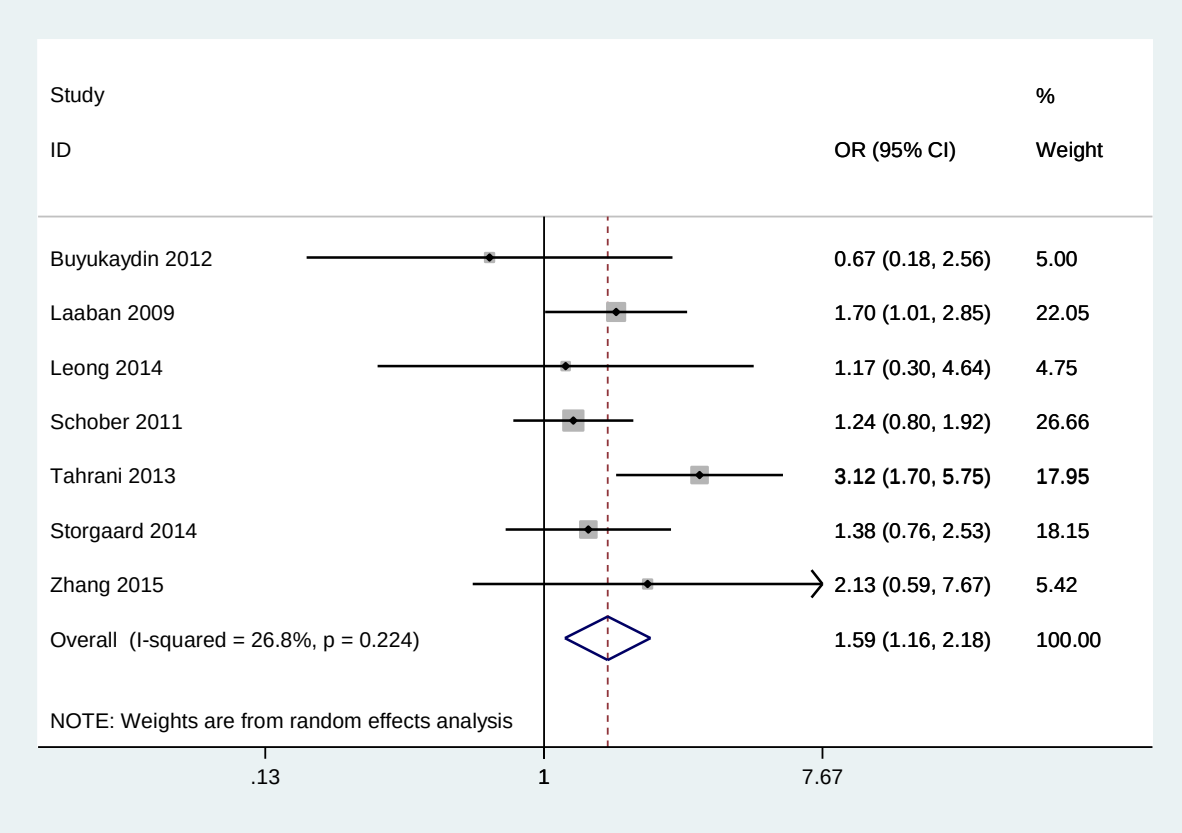


**Figure 1:** Forest plot of the association between obstuctive sleep apnea and diabetic kidney disease using results from studies which reported unadjusted odds ratios and 95% confidence intervals. Random effects analysis performed using Stata 13. Fixed effects model yielded similar results (pooled OR 1.60, 95% CI: 1.25 to 2.05, $I^2$=26.8%)

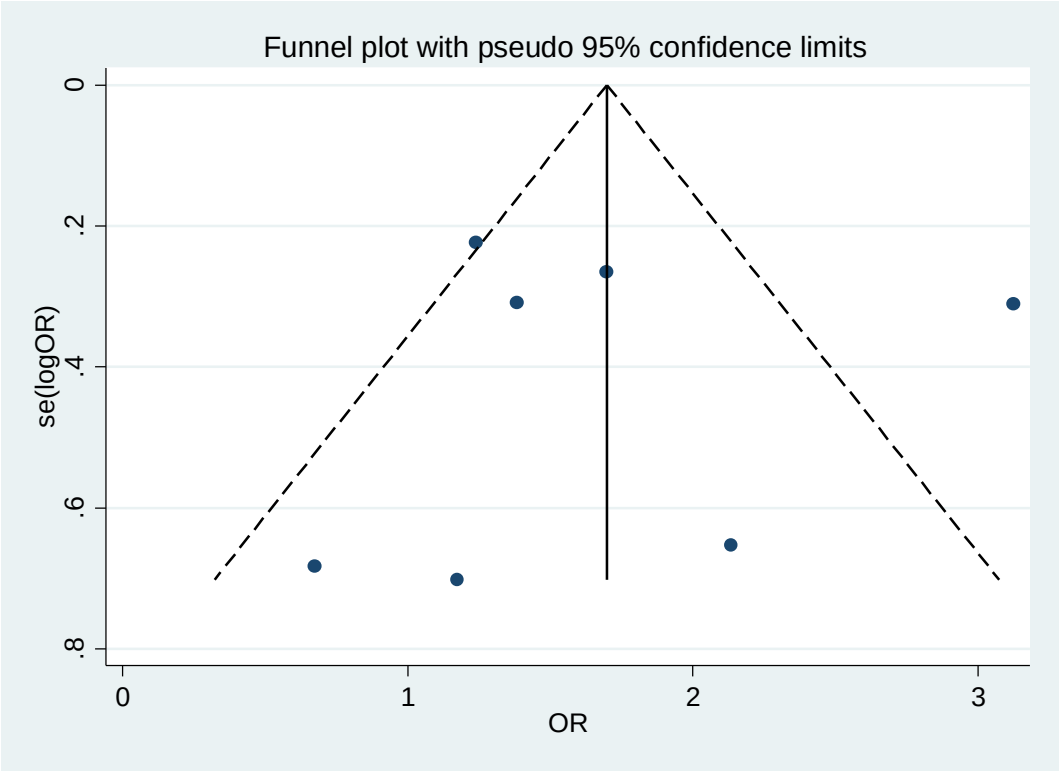


**Figure 2:** Funnel plot on studies which reported unadjusted odds ratios.

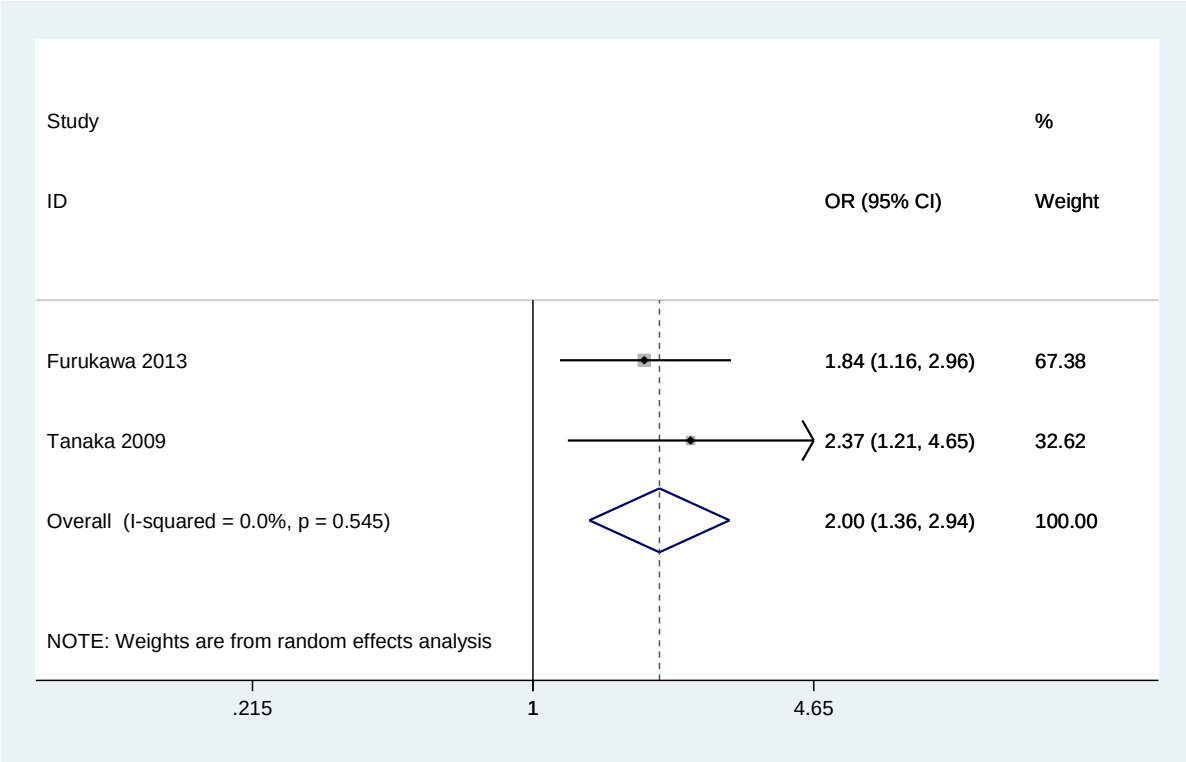


**Figure 3:** Forest plot of the association between obstuctive sleep apnea diagonsed using ODI and diabetic kidney disease using results from studies which reported adjusted odds ratios and 95% confidence intervals.

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